Radiological and clinical evaluation of cockayne syndrome: A case report

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ABSTRACT

Cockayne syndrome (CS) is a rare autosomal recessive disorder characterized by premature ageing (progeria), facial anomalies, cachectic dwarfism, mental retardation, cutaneous photosensitivity, and retinopathy, loss of adipose tissue and muscle, and neurological abnormality which are associated with the changes in the brain parenchyma. The findings of computed tomography scan and especially magnetic resonance imaging of the brain support the clinical diagnosis of CS. There is no permanent cure of this condition and death usually occurs in the 2nd or 3rd decade due to functional disability and multiple infections.

Key words: *Brain, Cockayne syndrome, Magnetic resonance imaging, Progeria*

Cockayne syndrome (CS) is a rare autosomal recessive disorder occurs in about 1 case per 2.77 million births [1]. It was first described by Cockayne in 1936, and till now, around 150 cases have been reported in literature [2]. CS is associated with mutations in the gene CS Type A (CSA)/excision-repair cross-complementing protein (ERCC) 8 or CS Type B (CSB)/ERCC6 which provide instructions for repairing damaged DNA [3]. Clinically, three types of CS have been described in literature as classical, milder, and severe form depending on the time of presentation and severity of the clinical symptoms and final outcome [4]. The classical features of CS are progressive loss of subcutaneous fat and muscle, mental retardation, premature ageing, dwarfism, facial abnormalities, microcephaly, retinopathy, protruding neck, hearing loss, dental changes, large extremities, joints contracture, photosensitivity, dry skin, and hair [5]. Intracranial calcification and brain atrophy are seen in most of the individuals. Progression of syndrome leads to functional disability and bedridden in the 2nd decade of life and patients lastly die [6]. Early diagnosis is very important for patient management and proper parental genetic counseling. We present a case which is still worth important as a rare entity with its important clinical and radiological findings.

CASE REPORT

A 19-year-old male along with his father came in the neuromedicine outpatient department with complaints of progressive developmental delay, mental retardation, unable to walk and frequent falls when attempted, cachectic dwarfism in the form of short stature, loss of subcutaneous fat and muscles volume, microcephaly, and infrequent seizures. Dryness of skin and hair noted; however, no deformity of limbs was seen.

Eye and otorhinolaryngology examinations showed features of sensorineural hearing loss and visual field defects (retinitis pigmentosa). Ultrasonography of the whole abdomen was normal except loss of volume of intra-abdominal fat. The patient had a computed tomography scan of brain, done long ago, showing only soft basal ganglia calcification with subtle cortical sulci prominence. This time, the patient was advised for magnetic resonance imaging (MRI) of the brain and correlated for the same. MRI brain revealed severe diffuse cerebral cortical and periventricular white matter atrophy, cerebellar atrophy, widened all ventricles, thinned corpus callosum, bilateral basal ganglia calcifications, and diffuse atrophy of the brain stem (Figs. 1-3). Diffuse hyperintense T2-weighted/fluid-attenuated inversion recovery (FLAIR) change in cerebral white matter reflecting hypomyelination/demyelination was also noted (Fig. 4).

These typical MRI findings with early onset bilateral basal ganglia calcification noted in gradient sequence and T1-weighted sequences (Figs. 2 and 3) and classical clinical features (Fig. 5) supported the diagnosis of CS. The parents of the patient have been explained the prognosis of the disorder and advised for the general care of patient according to the symptoms.

DISCUSSION

CS is an autosomal recessive disorder with incidence around 1 case per 2.77 million births [1]. The basic pathology is deficient DNA repair mechanism due to mutation in gene CSA/ERCC8 and CSB/ERCC6 located on the chromosomes 5 and 10, respectively [3]. Despite these, principle genes sensitivity of the patient fibroblasts

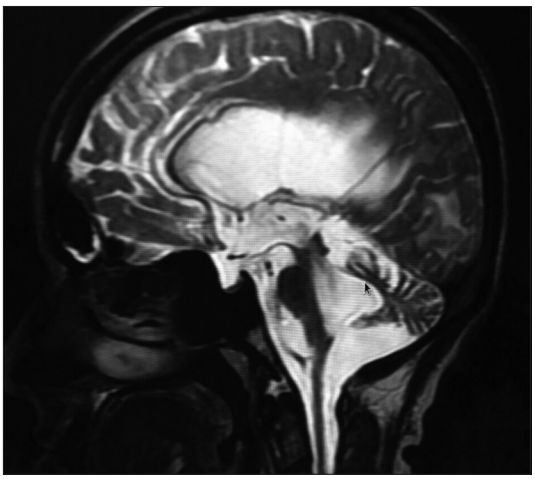

Figure 1: MRI T2W sagittal image showing diffuse atrophy of cerebrum, cerebellum, and brain stem. Ventricles are widely dilated secondary to brain atrophy, and bulging and thinned corpus callosum

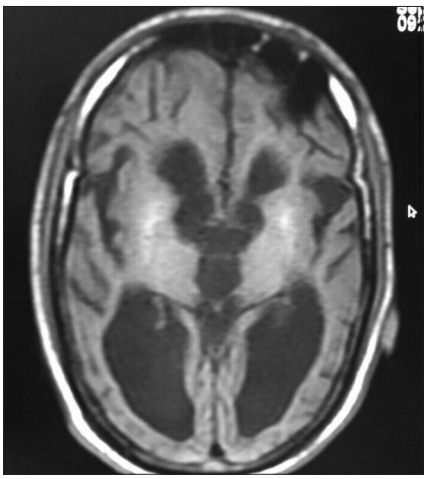

Figure 4: MRI T1W axial image showing diffuse cerebral atrophy, dilated ventricles, decreased volume of gray and white matter, and bilateral symmetrical hyperintense changes in basal ganglia due to soft calcification

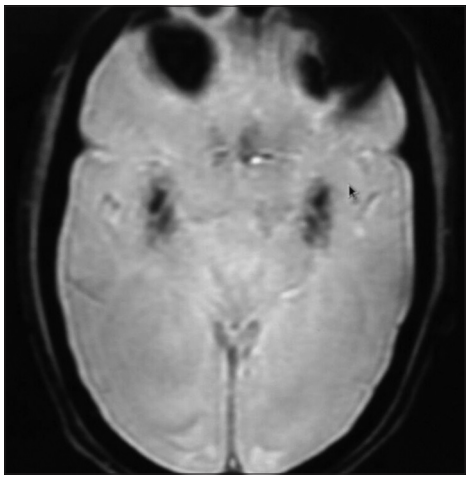

Figure 2: MRI GRADIENT axial image showing bilateral basal ganglia calcification

Figure 5: A 19-year-old patient with "Cockayne syndrome" showing sunken eyes, protruding nose, reduced height (dwarfism), decreased subcutaneous fat and muscle volume, and inability to stand without support

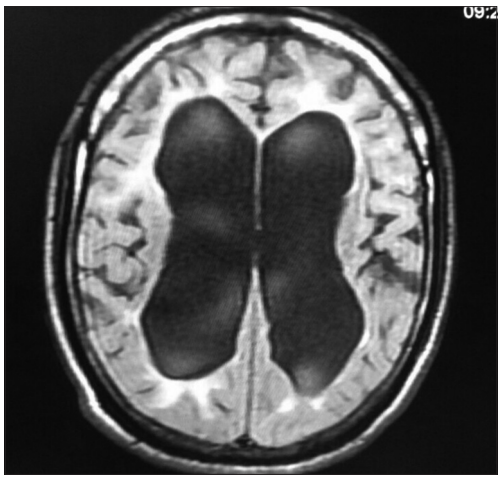

Figure 3: MRI T2 FLAIR axial image showing diffuse cerebral atrophy and white matter hyperintensity representing demyelination/ hypomyelination of white matter

to ultraviolet C irradiation has been considered the diagnostic test of choice [7]. Important feature in CS is that in spite of deficient DNA repair, patients do not develop cancer. The CS consists of progressive neurodegeneration, mental retardation, progeria, ataxia, dwarfism, facial dysmorphism, microcephaly, abnormal photosensitivity, hearing loss, and joints contracture [5,8].

CS is a rare entity and around 150 cases have been reported in literature up till now [2]. Male-to-female ratio is 4:1. This syndrome does not get over until 4–5 years of age where growth and development almost appear normal and after that manifestation of progressive neurodegenerative changes become evident. Most of the patients live up to the 2nd decade and finally die due to severe respiratory and other infections [6].

Three types of CS described in the literature. Type I is the classical form and includes majority of the patients and present with normal fetal growth and onset of abnormality in the 1st 2 years of life. Peripheral and central nervous systems progressively degenerate until death in the 1st or 2nd decade of life due to severe neurological disorders. Cortical atrophy is not severe in this type. Type II is severe form present since birth. Neurological development is very poor after birth and death

usually occurs around the age of seven [4]. This is also called as Cerebro-oculo-facio-skeletal syndrome [4]. Brain shows more severe damage including reduced myelination of white matter and more widespread calcification in the basal ganglia and cortex [9]. Type III is the milder form characterized by the late onset slow progression and these patients live up to adulthood [4].

Failure to thrive and neurological disorder are criteria for the diagnosis while photosensitivity, ophthalmic changes, sensorineural deafness, and dental disorder are other very common manifestation [10]. The neurologic changes are neuronal and myelin loss with calcium and iron deposition in the small vessels of the basal ganglia, cerebrum, and cerebellum. This neurodegeneration commonly presents as progressive mental retardation and ataxic gait. The other classical features are retinitis pigmentosa and photosensitive dermatosis. Neuroimaging including CT scan and MRI (T2 weighted and FLAIR) is the modality of choice for evaluation of brain.

MRI of the brain shows atrophy of the brain in supratentorial and infratentorial aspect along with hyperintense signal of the cerebral white matter on T2-weighted and FLAIR images representing hypomyelination/demyelination [11,12]. Early age basal ganglia calcification also prompts toward the syndrome along with cerebral and cerebellum calcification [10]. MRI results are compatible with diffuse cerebral white matter demyelination showing abnormal signal change.

The MRI of our patient also showed severe diffuse atrophy of cerebral, cerebellar, and brain stem causing marked dilatation of all ventricles and cerebrospinal fluid cisterns with cerebral white matter demyelination, bilateral basal ganglia calcification and clinical features of severe mental retardation, severe gait abnormality, and cachectic dwarfism. However, it was difficult to differentiate the CS from other white matter diseases in the absence of basal ganglia calcification. In the appropriate clinical setting, MRI features of brain atrophy, white matter changes and bilateral cerebral and basal ganglia calcification are sufficient to support the diagnosis.

No permanent cure of this disorder and patient treated according to their symptomatology. Genetic counseling of the parents is advised as the disorder has about 25% chance of penetration into any future offspring [10].

CONCLUSION

CS is rare disorder and diagnosis of CS can easily be made by the classical clinical manifestation along with typical brain changes in the radiological evaluation. MRI plays an important role in this regard showing demyelination of white matter, diffuse brain atrophy, and bilateral basal ganglia calcification as a hallmark changes in CS.

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